REMARKS

The present Response and Request for Reconsideration is being submitted in reply to the Advisory Action mailed October 3, 2007 and the Interview conducted on the same date.

Applicants respectfully request entry of the Amendment filed September 11, 2007 and reconsideration of the proposed claim amendments and arguments presented therein. The entire Amendment filed September 11, 2007 and the arguments presented therein are incorporated herein by reference.

I. Response to Advisory Action

A. Request for Reconsideration and Entry of the Previously Filed Amendment on September 11, 2007

The Advisory Action dated October 3, 2007 indicates that the Amendment filed September 11, 2007 was not entered because the amendments to the claims raise new issues that would require further consideration and/or search by the Examiner. Additionally, the Examiner states they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal. Specifically, in the "note" the Examiner states that the limitation of the amount of pirfenidone in the claims would require further search and consideration.

Applicants respectfully submit that the proposed claim amendments do not raise a new issue since the amendment merely defines the original claimed range by deleting the word "about". Thus, the presently claimed range of the concentration of pirfenidone in the composition of the present invention is essentially the same as originally claimed, i.e., 10% to 25%. For at least this reason, the proposed claim amendments should be entered since no new

issues are raised which require further search and/or consideration and because they place the claims in better form for appeal.

Even further, the proposed claim amendments at least reduce the issues for appeal. While entry of an amendment after final rejection is not a matter of right, the rules provide for entry of amendments after final rejection where the amendment adopts Examiner suggestions, removes issues for appeal, or in some other way requires only a cursory review by the Examiner. See 37 C.F.R. § 1.116 (b) (1) and (2) and MPEP § 714.13(II).

The test for determining whether an amendment should be entered is whether the claims, if amended as proposed, would avoid any of the rejections set forth in the last Office action. See MPEP § 714.13(III). In this regard, the proposed claim amendments clearly overcome the §102 rejection based on Scheiwe et al.

As pointed out in the Amendment filed on September 11, 2007, Scheiwe et al discloses that the amount of the active ingredient, i.e., pirfenidone, is preferably within the range of about 0.5% to about 9% by weight, preferably from about 3% to about 7% by weight of the entire composition. Column 2, lines 31-37. Thus, the range taught by Scheiwe et al is <u>not</u> within the presently claimed range and therefore does not constitute anticipation within the meaning of §102. Anticipation under §102 can be found only when the reference discloses exactly what is claimed. A reference which teaches a value or range that is close to, but does not overlap or touch, the claimed range does not anticipate the claimed range. See MPEP § 2131.03(III). In this case, the reference does not disclose an example wherein the active ingredient of the composition, i.e., pirfenidone, is employed in an amount of 10% to about 25%. To the contrary, the Scheiwe et al discloses that typical formulation and preferred formulations contain 3 to 7

wt% of the active ingredient, which is not close to the recited range of "10% to about 25%". Thus, for at least these reasons, Scheiwe et al does not anticipate the presently claimed invention.

Since the proposed amendments would overcome the §102 rejection based on Scheiwe et al, the proposed amendment would at least remove issues for appeal. Thus, for this additional reason, the proposed claim amendments should be entered.

Accordingly, Applicants respectfully request entry of the proposed Amendment filed September 11, 2007.

B. Request for Reconsideration of the Art Rejections.

The Examiner did not specifically mention the §102 rejection based on Scheiwe et al in the Advisory Action. However, Scheiwe et al does not identically disclose the present invention as recited in the amended claims for the reasons set forth above. Thus, Applicants respectfully request withdrawal of the rejection.

With respect to the §103 art rejections, the Examiner takes the position that Margolin teaches an ointment, which can be a liquid, inhalable fluids, eye drops (which are liquids) and therefore it is reasonable to conclude that the composition comprises a solvent which is able to dissolve the pyridones as claimed.

Additionally, regarding the §103 rejection based on Margolin in view of Iyer et al, the Examiner relies on Iyer et al as generally teaching that specific solvents may be used for poorly soluble drugs. The Examiner concludes that it is reasonable to conclude that one of ordinary skill in the art would look to prior art to determine suitable solvents to use to dissolve a drug when formulating a composition that class for a poorly soluble drug to be dissolved.

Applicants respectfully traverse the rejection for the reasons of record as set forth in the Amendment filed on September 11, 2007 and further in view of the following.

Applicants note that the Margolin generally teaches examples of medical preparations include (1) capsules, (2) tablets, (3) powders, (4) granules, (5) syrups, (6) injections (i.v, i.m. or drip administration), (7) cream, (8) ointment, (9) inhalation and (10) eye drops, (11) suppositories, (12) pills, etc., and some of these dosage forms might reasonably be expected to be liquids. See page 20. However, Margolin does not specifically disclose an example of a "liquid" preparation including pirfenidone in the amount presently claimed.

Margolin specifically exemplifies an ointment comprising 5 to 10% pirfenidone (see page 21) which the Examiner states might be considered a "liquid". However, ointments are generally defined as "semisolids". Indeed Margolin refers to "hydrophilic ointment", which is not a "liquid" composition based on its formulation (see for example, Scheiwe et al at paragraph [0081] and Remington's Pharmaceutical Sciences, 17th Ed., page 1304 copy attached as Attachment "A"). Additionally, there is no teaching or suggestion within the reference to indicate that the ointment taught by Margolin is a "liquid" instead of a "semisolid" ointment. Also, there is no teaching or guidance in Margolin for obtaining a liquid composition containing a high concentration of pirfenidone as recited in the present claims.

Specifically, Margolin does not "teach" one of ordinary skill in the art to make and/or use a liquid composition comprising a high concentration of pirfenidone within the range recited in the present claims. Margolin merely lists a number of theoretical dosage forms, which are applicable to most active ingredients, without any indication as to how to prepare such dosage

forms and which inactive ingredients or excipients to use. Also, Margolin does not exemplify any specific "liquid preparations" or suitable solvents for nay such preparations. Therefore, Margolin is not enabling for one of ordinary skill in the art to arrive at the present invention.

Even further, the example of an ointment "comprising 5 to 10% pirfenidone" does not provide one of ordinary skill in the art with guidance or indication as to how to make the disclosed ointment and which inactive ingredients to use. By definition, an "ointment" is not a "liquid" as mentioned above. However, "ointments" are semisolid preparations for external application to the skin or mucous membranes (see definition in the attached copy from The United States Pharmacopeia, Pharmaceutical Dosage Forms, pages 1944-1946; Attachment "B").

Ointments, by definition, so-called water-removable ointments such as hydrophilic ointment can be formed only if the ingredients used can be dissolved in water (see the Example in Remington's Pharmaceutical Sciences, 17th Ed., page 1304 (Attachment "A")). In case the ingredients are dissolved in an organic solvent, it cannot form any (hydrophilic) ointment since all the emulgators necessary for making the ointment (or creams) will also be dissolved and not form the semisolid emulsion ointment.

The bottom line is that Margolin does not provide any examples or a teaching of how to make any of the dosage forms named, nor any components or ingredients necessary to make such preparations. Thus, Margolin is not enabling for a liquid composition as presently claims and the present invention is not rendered obvious by Margolin.

Further, none of the cited references remedies the deficiencies of Margolin.

Regarding the §103 rejection based on Margolin in view of Iyer et al, there is no apparent reason for one of ordinary skill in the art to combine the references as suggested by the Examiner since the references do not involve the same or similar active ingredients and do not teach liquid compositions containing an amount of pirfenidone within the claimed range. Further, neither of Margolin and Iyer et al recognize the problem of obtaining a liquid composition having a high concentration of pirfenidone within the claimed range. Thus, the presently claimed invention would not have been obvious over the combination of Margolin in view of Iyer et al.

Regarding the §103 rejection based on Scheiwe et al, Applicants submit that Scheiwe et al does not identically disclose all elements of the present invention for the reasons mentioned above. Specifically, Scheiwe et al describes a formulation of oil-in-water emulsion-cream containing pirfenidone on an amount of 3% to 7% by weight of said composition, but preferably in the range of about 0.5% to about 9% by weight. Hence, Scheiwe et al does not disclose, teach or suggest pirfenidone in a concentration of 10% to about 25%" and Iyer et al does not remedy this deficiency.

Iyer et al does not disclose, teach or suggest a liquid composition comprising pirfenidone. Iyer et al teaches gelatin capsules comprising loratidine. Iyer et al specifically describes a formulation of loratidine, solubilized in a mixture of solvent and emulsifiers and which is specifically to be used in making soft gelatin capsules of this particular drug. The maximum concentration of the drug (as shown in Table 1 at paragraph [0030]) reached in the solvent mixture is 8% drug. The use of Transcutol P alone as a solvent is not specified, and it is only one component along with a mixture of other components of the formulation (for making soft

gelatin capsules of loratidine). Hence, Iyer et al does not teach or suggest the presently claimed invention and does not remedy the deficiencies of Scheiwe.

Thus, one of ordinary skill in the art would not have been motivated to combine the references with a reasonable expectation of success.

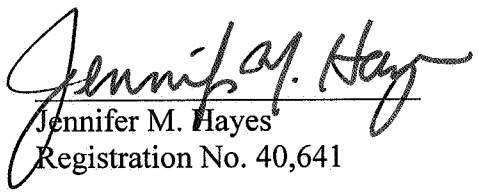
In view of the above, Applicants respectfully request entry of the Amendment previously filed on September 11, 2007 and reconsideration and withdrawal of the objection to claim 9 and the §102 and §103 art rejections.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Jennifer M. Hayes
Registration No. 40,641

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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Date: November 2, 2007

Remington's Pharmaceutical Sciences

17

Cetyl Alcohol

Cetostearyl Alcohol; "Palmityl" Alcohol; Aldol 52 (*Sherex*)

$CH_3(CH_2)_{14}CH_2OH$

1-Hexadecanol [124-29-8] $C_{16}H_{34}O$ (242.44); a mixture of not less than 90% of cetyl alcohol, the remainder chiefly stearyl alcohol.

Preparation—By catalytic hydrogenation of palmitic acid, or saponification of spermaceti, which contains cetyl palmitate.

Description—Unctuous, white flakes, granules, cubes, or castings, having a faint characteristic odor and a bland, mild taste; melts between 45° and 50° and not less than 90% distils between 316° and 336°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, ether, and vegetable oils.

Uses—Similar to *Stearyl Alcohol* (page 1300). Cetyl alcohol also imparts a smooth texture to the skin, and is widely used in cosmetic creams and lotions.

Cold Cream

Petrolatum Rose Water Ointment USP XVI

Cetyl Esters Wax	125 g
White Wax	120 g
Mineral Oil	560 g
Sodium Borate	5 g
Purified Water	190 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath with the mineral oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has congealed.

If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

Uses—Useful as an emollient, cleansing cream, and ointment base. It resembles *Rose Water Ointment*, differing only in that mineral oil is used in place of almond oil and omitting the fragrance. This change produces an ointment base which is not subject to rancidity like one containing a vegetable oil. This is a water-in-oil emulsion.

Glyceryl Monostearate

Octadecanoic acid, monoester with 1,2,3-propanetriol

Monostearin [31566-31-1]; a mixture chiefly of variable proportions of glyceryl monostearate [$C_3H_5(OH)_2C_{18}H_{35}O_2$ = 358.56] and glyceryl monopalmitate [$C_3H_5(OH)_2C_{16}H_{31}O_2$ = 330.51].

Preparation—Among other ways, by reacting glycerin with commercial stearoyl chloride.

Description—White, wax-like solid or occurs in the form of white, wax-like beads, or flakes; slight, agreeable, fatty odor and taste; does not melt below 55°; affected by light.

Solubility—Insoluble in water, but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent; dissolves in hot organic solvents such as alcohol, mineral or fixed oils, benzene, ether, and acetone.

Uses—A thickening and emulsifying agent for ointments. See *Ointments* (page 1573).

Hydrophilic Ointment

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium Lauryl Sulfate	10 g
Propylene Glycol	120 g
Stearyl Alcohol	250 g
White Petrolatum	250 g
Purified Water	370 g
To make about	1000 g

Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75°. Add the other ingredients, previously dissolved in the water and warmed to 75°, and stir the mixture until it congeals.

Uses—A *water-removable ointment base* for the so-called "washable" ointments. This is an oil-in-water emulsion.

Lanolin

Hydrous Wool Fat

The purified, fat-like substance from the wool of sheep, *Ovis aries* Linné (Fam *Bovidae*); contains 25 to 30% water.

Description—Yellowish white, ointment-like mass, having a slight, characteristic odor; when heated on a steam bath it separates into an upper oily and a lower water layer; when the water is evaporated a residue of *Lanolin* remains which is transparent when melted.

Solubility—Insoluble in water; soluble in chloroform and ether with separation of its water.

Uses—Largely as a vehicle for ointments, for which it is admirably adapted, on account of its compatibility with skin lipids. It emulsifies aqueous liquids. Lanolin is a water-in-oil emulsion.

Rose Water Ointment

Cold Cream; Galen's Cerate

Cetyl Esters Wax	125 g
White Wax	120 g
Almond Oil	560 g
Sodium Borate	5 g
Stronger Rose Water	25 mL
Purified Water	165 mL
Rose Oil	0.2 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath, add the almond oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water and stronger rose water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has cooled to about 45°. Then incorporate the rose oil.

Rose water ointment must be free from rancidity. If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

History—Originated by Galen, the famous Roman physician-pharmacist of the 1st century AD, was known for many centuries by the name of *Unguentum* or *Ceratum Refrigerans*. It has changed but little in proportions or method of preparation throughout many centuries.

Uses—An *emollient* and *ointment base*. It is a water-in-oil emulsion.

Stearic Acid

Octadecanoic acid; Cetylacetic Acid; Stearophanic Acid

Stearic acid [57-11-4]; a mixture of stearic acid [$C_{18}H_{36}O_2$ = 284.48] and palmitic acid [$C_{16}H_{32}O_2$ = 256.43], which together constitute not less than 90.0% of the total content. The content of each is not less than 40.0% of the total.

Purified Stearic Acid USP is a mixture of the same acids which together constitute not less than 96.0% of the total content, and the content of $C_{18}H_{36}O_2$ is not less than 90.0% of the total.

Preparation—From edible fats and oils (see exception below) by boiling them with soda lye, separating the glycerin and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid is subsequently separated from any oleic acid by cold expression. It is also prepared by the hydrogenation and subsequent saponification of *olein*. It may be purified by recrystallization from alcohol.

Description—Hard, white or faintly yellowish somewhat glossy and crystalline solid, or a white or yellowish white powder; an odor and taste suggestive of tallow. Stearic acid melts at about 55.5° and should not congeal at a temperature below 54°; the purified acid melts at 69° and 70° and congeals between 66° and 69°; stearic acid slowly volatilizes between 90° and 100°.

Solubility—Practically insoluble in water; 1 g in about 20 mL alcohol, 2 mL chloroform, 3 mL ether, 25 mL acetone, or 6 mL carbon tetrachloride; freely soluble in carbon disulfide; also soluble in amyl acetate, benzene, and toluene.

Incompatibilities—Insoluble stearates are formed with many *metals*. Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when *zinc* or *calcium* salts are compounded therein.

Uses—In the preparation of sodium stearate which is the solidifying agent for the official glycerin suppositories, in enteric tablet

Appl. No. 10/540,422
Docket No. Q88273
Amdt. Dated November 2, 2007
Attachment B

1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 1995

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

EXTENDED-RELEASE CAPSULES

Extended-release capsules are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes and requirements for *Drug release* (see *Drug Release* ⟨724⟩) typically are specified in the individual monographs.

CREAMS

Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a relatively fluid consistency formulated as either water-in-oil (e.g., *Cold Cream*) or oil-in-water (e.g., *Fluocinolone Acetonide Cream*) emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable. Creams can be used for administering drugs via the vaginal route (e.g., *Triple Sulfa Vaginal Cream*).

ELIXIRS

See *Solutions*.

EMULSIONS

Emulsions are two-phase systems in which one liquid is dispersed throughout another liquid in the form of small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentrating in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalescence. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification upon mixing.

Natural, semisynthetic, and synthetic hydrophilic polymers may be used in conjunction with surfactants in oil-in-water emulsions as they accumulate at interfaces and also increase the viscosity of the aqueous phase, thereby decreasing the rate of formation of aggregates of droplets. Aggregation is generally accompanied by a relatively rapid separation of an emulsion into a droplet-rich and droplet-poor phase. Normally the density of an oil is lower than that of water, in which case the oil droplets and droplet aggregates rise, a process referred to as creaming. The greater the rate of aggregation, the greater the droplet size and the greater the rate of creaming. The water droplets in a water-in-oil emulsion generally sediment because of their greater density.

The consistency of emulsions varies widely, ranging from easily pourable liquids to semisolid creams. Generally oil-in-water creams are prepared at high temperature, where they are fluid, and cooled to room temperature, whereupon they solidify as a result of solidification of the internal phase. When this is the case, a high internal-phase volume to external-phase volume ratio is not necessary for semisolid character, and, for example, stearic acid creams or vanishing creams are semisolid with as little as 15% internal phase. Any semisolid character with water-in-oil emulsions generally is attributable to a semisolid external phase.

All emulsions require an antimicrobial agent because the aqueous phase is favorable to the growth of microorganisms. The presence of a preservative is particularly critical in oil-in-water emulsions where contamination of the external phase occurs readily. Since fungi and yeasts are found with greater frequency than bacteria, fungistatic as well as bacteriostatic properties are desirable. Bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and many natural stabilizers such as tragacanth and guar gum.

Complications arise in preserving emulsion systems, as a result of partitioning of the antimicrobial agent out of the aqueous phase

gredients that reduce effectiveness. Therefore, the effectiveness of the preservative system should always be tested in the final product. Preservatives commonly used in emulsions include methyl-, ethyl-, propyl-, and butyl-parabens, benzoic acid, and quaternary ammonium compounds.

See also *Creams* and *Ointments*.

EXTRACTS AND FLUIDEXTRACTS

Extracts are concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, by evaporation of all or nearly all of the solvent, and by adjustment of the residual masses or powders to the prescribed standards.

In the manufacture of most extracts, the drugs are extracted by percolation. The entire percolates are concentrated, generally by distillation under reduced pressure in order to subject the drug principles to as little heat as possible.

Fluidextracts are liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, and so made that, unless otherwise specified in an individual monograph, each mL contains the therapeutic constituents of 1 g of the standard drug that it represents.

A fluidextract that tends to deposit sediment may be aged and filtered or the clear portion decanted, provided the resulting clear liquid conforms to the Pharmacopeial standards.

Fluidextracts may be prepared from suitable extracts.

GELS

Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., *Aluminum Hydroxide Gel*). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., *Bentonite Magma*). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect. (See *Suspensions*.)

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (e.g., *Carbomer*) or from natural gums (e.g., *Tragacanth*). The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

Gels can be used to administer drugs topically or into body cavities (e.g., *Phenylephrine Hydrochloride Nasal Jelly*).

IMPLANTS (PELLETS)

Implants or pellets are small sterile solid masses consisting of a highly purified drug (with or without excipients) made by compression or molding. They are intended for implantation in the body (usually subcutaneously) for the purpose of providing continuous release of the drug over long periods of time. Implants are administered by means of a suitable special injector or surgical incision. This dosage form has been used to administer hormones such as testosterone or estradiol. They are packaged individually in sterile vials or foil strips.

INFUSIONS, INTRAMAMMARY

Intramammary infusions are suspensions of drugs in suitable oil vehicles. These preparations are intended for veterinary use only, and are administered by instillation via the teat canals into the udders of milk-producing animals.

INHALATIONS

Inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory

Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer or the nebulizer may be attached to a plastic face mask, tent, or intermittent positive pressure breathing (IPPB) machine.

Another group of products, also known as metered-dose inhalers (MDIs) are propellant driven drug suspensions or solutions in liquified gas propellant with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single-dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation.

Examples of MDIs containing drug solutions and suspensions in this pharmacopeia are *Epinephrine Inhalation Aerosol* and *Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol*, respectively.

Powders may also be administered by mechanical devices that require manually produced pressure or a deep inhalation by the patient (e.g., *Cromolyn Sodium for Inhalation*).

A special class of inhalations termed inhalants consists of drugs or combination of drugs, that by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant generally is administered is known as an inhaler.

INJECTIONS

See *Injections* ⟨1⟩.

IRRIGATIONS

Irrigations are sterile solutions intended to bathe or flush open wounds or body cavities. They are used topically, never parenterally. They are labeled to indicate that they are not intended for injection.

LOTIONS

See *Solutions* or *Suspensions*.

LOZENGES

Lozenges are solid preparations, which are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments, usually in a flavored, sweetened base. They can be prepared by molding (gelatin and/or fused sucrose or sorbitol base) or by compression of sugar based tablets. Molded lozenges are sometimes referred to as pastilles while compressed lozenges are often referred to as troches. They are usually intended for treatment of local irritation or infections of the mouth or throat but may contain active ingredients intended for systemic absorption after swallowing.

OINTMENTS

Ointments are semisolid preparations intended for external application to the skin or mucous membranes.

Ointment bases recognized for use as vehicles fall into four general classes: the hydrocarbon bases, the absorption bases, the water-removable bases, and the water-soluble bases. Each therapeutic ointment possesses as its base a representative of one of these four general classes.

Hydrocarbon Bases

These bases, which are known also as "oleaginous ointment bases," are represented by *White Petrolatum* and *White Ointment*. Only small amounts of an aqueous component can be incorporated into them. They serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. Hydrocarbon bases are used chiefly for their emollient effects, and are difficult to wash off. They do not "dry out" or change noticeably on aging.

Absorption Bases

This class of bases may be divided into two groups: the first group consisting of bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (*Hydrophilic Petrolatum* and *Lanolin*), and the second group consisting of water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (*Lanolin*). Absorption bases are useful also as emollients.

Water-removable Bases

Such bases are oil-in-water emulsions, e.g., *Hydrophilic Ointment*, and are more correctly called "creams." (See *Creams*.) They are also described as "water-washable," since they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic reasons. Some medicaments may be more effective in these bases than in hydrocarbon bases. Other advantages of the water-removable bases are that they may be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

Water-soluble Bases

This group of so-called "greaseless ointment bases" is comprised of water-soluble constituents. *Polyethylene Glycol Ointment* is the only Pharmacopeial preparation in this group. Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly called "Gels." (See *Gels*.)

Choice of Base—The choice of an ointment base depends upon many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and the requisite shelf-life of the finished product. In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases containing water, even though they may be more effective in the latter.

OPHTHALMIC PREPARATIONS

Drugs are administered to the eyes in a wide variety of dosage forms, some of which require special consideration. They are discussed in the following paragraphs.

Ointments

Ophthalmic ointments are ointments for application to the eye. Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions and meet the requirements under *Sterility Tests* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility Tests* ⟨71⟩, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use, unless otherwise directed in the individual monograph, or unless the formula itself is bacteriostatic (see *Added Substances* under *Ophthalmic Ointments* ⟨771⟩). The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* under *Ophthalmic Ointments* ⟨771⟩. The immediate containers for ophthalmic ointments shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic ointments be sealed and tamper-proof so that sterility is assured at time of first use.

The ointment base that is selected must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye, and retain the activity of the medicament for a reasonable period under proper storage conditions.

Petrolatum is mainly used as a base for ophthalmic drugs. Some absorption bases, water-removable bases, and water-soluble

bases may be desirable for water-soluble drugs. Such bases allow for better dispersion of water-soluble medicaments, but they must be nonirritating to the eye.

Solutions

Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Preparation of an ophthalmic solution requires careful consideration of such factors as the inherent toxicity of the drug itself, isotonicity value, the need for buffering agents, the need for a preservative (and, if needed, its selection), sterilization, and proper packaging. Similar considerations are also made for nasal and otic products.

ISOTONICITY VALUE

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort.

Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient(s) strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lacrimal fluid takes place rapidly so that discomfort from the hypertonicity is only temporary. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes; it is therefore important that solutions used for this purpose be approximately isotonic.

BUFFERING

Many drugs, notably alkaloidal salts, are most effective at pH levels that favor the undissociated free bases. At such pH levels, however, the drug may be unstable so that compromise levels must be found and held by means of buffers. One purpose of buffering some ophthalmic solutions is to prevent an increase in pH caused by the slow release of hydroxyl ions by glass. Such a rise in pH can affect both the solubility and the stability of the drug. The decision whether or not buffering agents should be added in preparing an ophthalmic solution must be based on several considerations. Normal tears have a pH of about 7.4 and possess some buffer capacity. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity. Where only 1 or 2 drops of a solution containing them are added to the eye, the buffering action of the tears is usually adequate to raise the pH and prevent marked discomfort. In some cases pH may vary between 3.5 and 8.5. Some drugs, notably pilocarpine hydrochloride and epinephrine bitartrate, are more acid and overtax the buffer capacity of the lacrimal fluid. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. This is not usually possible since, at pH 7.4, many drugs are not appreciably soluble in water. Most alkaloidal salts precipitate as the free alkaloid at this pH. Additionally, many drugs are chemically unstable at pH levels approaching 7.4. This instability is more marked at the high temperatures employed in heat sterilization. For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration.

An ophthalmic preparation with a buffer system approaching the physiological pH can be obtained by mixing a sterile solution of the drug with a sterile buffer solution using aseptic technique. Even so, the possibility of a shorter shelf-life at the higher pH must be taken into consideration, and attention must be directed toward the attainment and maintenance of sterility throughout the manipulations.

Many drugs, when buffered to a therapeutically acceptable pH, would not be stable in solution for long periods of time. These products are lyophilized and are intended for reconstitution immediately before use (e.g., *Acetylcholine Chloride for Ophthalmic Solution*).

STERILIZATION

The sterility of solutions applied to an injured eye is of the greatest importance. Sterile preparations in special containers for individual use on one patient should be available in every hospital, office, or other installation where accidentally or surgically traumatized eyes are treated. The method of attaining sterility is determined primarily by the character of the particular product (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩).

Whenever possible, sterile membrane filtration under aseptic conditions is the preferred method. If it can be shown that product stability is not adversely affected, sterilization by autoclaving in the final container is also a preferred method.

Buffering certain drugs near the physiological pH range makes them quite unstable at high temperature.

Avoiding the use of heat by employing a bacteria-retaining filter is a valuable technique, provided caution is exercised in the selection, assembly, and use of the equipment. Single-filtration, presterilized disposable units are available and should be utilized wherever possible.

PRESERVATION

Ophthalmic solutions may be packaged in multiple-dose containers when intended for the individual use of one patient and where the ocular surfaces are intact. It is mandatory that the immediate containers for ophthalmic solutions be sealed and tamper-proof so that sterility is assured at time of first use. Each solution must contain a suitable substance or mixture of substances to prevent the growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use.

Where intended for use in surgical procedures, ophthalmic solutions, although they must be sterile, should not contain antibacterial agents, since they may be irritating to the ocular tissues.

THICKENING AGENT

A pharmaceutical grade of methylcellulose (e.g., 1% if the viscosity is 25 centipoises, or 0.25% if 4000 centipoises) or other suitable thickening agents such as hydroxypropyl methylcellulose or polyvinyl alcohol occasionally are added to ophthalmic solutions to increase the viscosity and prolong contact of the drug with the tissue. The thickened ophthalmic solution must be free from visible particles.

Suspensions

Ophthalmic suspensions are sterile liquid preparations containing solid particles dispersed in a liquid vehicle intended for application to the eye (see *Suspensions*). It is imperative that such suspensions contain the drug in a micronized form to prevent irritation and/or scratching of the cornea. Ophthalmic suspensions should never be dispensed if there is evidence of caking or aggregation.

Strips

Fluorescein sodium solution should be dispensed in a sterile, single-use container or in the form of a sterile, impregnated paper strip. The strip releases a sufficient amount of the drug for diagnostic purposes when touched to the eye being examined for a foreign body or a corneal abrasion. Contact of the paper with the eye may be avoided by leaching the drug from the strip onto the eye with the aid of sterile water or sterile sodium chloride solution.

PASTES

Pastes are semisolid dosage forms that contain one or more drug substances intended for topical application. One class is made from a single phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*), consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes appear less greasy and more absorptive than ointments by reason of a high proportion of drug substance(s) having an affinity for water. These pastes tend to absorb serum

addition, some physical changes not necessarily related to chemical potency, such as change in color and odor, or formation of a precipitate, or clouding of solution, may serve to alert the pharmacist to the possibility of a stability problem. It should be assumed that a product that has undergone a physical change not explained in the labeling may also have undergone a chemical change and such a product is never to be dispensed. Excessive microbial growth and/or contamination also may appear as a physical change. A gross change in a physical characteristic such as color or odor is a sign of instability in any product. Other common physical signs of deterioration of dosage forms include the following.

SOLID DOSAGE FORMS—Many solid dosage forms are designed for storage under low-moisture conditions. They require protection from environmental water, and therefore should be stored in tight containers (see *Containers* in the *General Notices*) or in the container supplied by the manufacturer. The appearance of fog or liquid droplets, or clumping of the product, inside the container signifies improper conditions. The presence of a desiccant inside the manufacturer's container indicates that special care should be taken in dispensing. Some degradation products, for example, salicylic acid from aspirin, may sublime and be deposited as crystals on the outside of the dosage form or on the walls of the container.

Hard and Soft Gelatin Capsules—Since the capsule formulation is encased in a gelatin shell, a change in gross physical appearance or consistency, including hardening or softening of the shell, is the primary evidence of instability. Evidence of release of gas, such as a distended paper seal, is another sign of instability.

Uncoated Tablets—Evidence of physical instability in uncoated tablets may be shown by excessive powder and/or pieces (i.e., crumbling as distinct from breakage) of tablet at the bottom of the container (from abraded, crushed, or broken tablets); cracks or chips in tablet surfaces; swelling; mottling; discoloration; fusion between tablets; or the appearance of crystals that obviously are not part of the tablet itself on the container walls or on the tablets.

Coated Tablets—Evidence of physical instability in coated tablets is shown by cracks, mottling, or tackiness in the coating and the clumping of tablets.

Dry Powders and Granules—Dry powders and granules that are not intended for constitution into a liquid form in the original container may cake into hard masses or change color, which may render them unacceptable.

Powders and Granules Intended for Constitution as Solutions or Suspensions—Dry powders and granules intended for constitution into solutions or suspensions require special attention. Usually such forms are those antibiotics or vitamins that are particularly sensitive to moisture. Since they are always dispensed in the original container, they generally are not subject to contamination by moisture. However, an unusual caked appearance necessitates careful evaluation, and the presence of a fog or liquid droplets inside the container generally renders the preparation unfit for use. Presence of an objectionable odor also may be evidence of instability.

Effervescent Tablets, Granules, and Powders—Effervescent products are particularly sensitive to moisture. Swelling of the mass or development of gas pressure is a specific sign of instability, indicating that some of the effervescent action has occurred prematurely.

LIQUID DOSAGE FORMS—Of primary concern with respect to liquid dosage forms are homogeneity and freedom from excessive microbial contamination and growth. Instability may be indicated by cloudiness or precipitation in a solution, breaking of an emulsion, nonresuspendable caking of a suspension, or organoleptic changes. Microbial growth may be accompanied by discoloration, turbidity, or gas formation.

Solutions, Elixirs, and Syrups—Precipitation and evidence of microbial or chemical gas formation are the two major signs of instability.

Emulsions—The breaking of an emulsion (i.e., separation of an oil phase that is not easily dispersed) is a characteristic sign of instability; this is not to be confused with creaming, an easily redispersible separation of the oil phase that is a common occurrence with stable emulsions.

Suspensions—A caked solid phase that cannot be resuspended by a reasonable amount of shaking is a primary indication of instability in a suspension. The presence of relatively large particles may mean that excessive crystal growth has occurred.

Tinctures and Fluidextracts—Tinctures, fluidextracts, and similar preparations usually are dark in color because they are concentrated, and thus they should be scrutinized carefully for evidence of precipitation.

Sterile Liquids—Maintenance of sterility is of course critical for sterile liquids. The presence of microbial contamination in sterile liquids usually cannot be detected visually, but any haze, color change, cloudiness, surface film, particulate or flocculent matter, or gas formation is sufficient reason to suspect possible contamination. Clarity of sterile solutions intended for ophthalmic or parenteral use is of utmost importance. Evidence that the integrity of the seal has been violated on such products should make them suspect.

SEMISOLIDS (CREAMS, OINTMENTS, AND SUPPOSITORIES)—For creams, ointments, and suppositories, the primary indication of instability is often either discoloration or a noticeable change in consistency or odor.

Creams—Unlike ointments, creams usually are emulsions containing water and oil. Indications of instability in creams are emulsion breakage, crystal growth, shrinking due to evaporation of water, and gross microbial contamination.

Ointments—Common signs of instability in ointments are a change in consistency and excessive "bleeding" (i.e., separation of excessive amounts of liquid) and formation of granules or grittiness.

Suppositories—Excessive softening is the major indication of instability in suppositories, although some suppositories may dry out and harden or shrivel. Evidence of oil stains on packaging material should warn the pharmacist to examine individual suppositories more closely by removing any foil covering if necessary. As a general rule (although there are exceptions), suppositories should be stored in a refrigerator (see *Storage Temperature* in the *General Notices*).

Proper Treatment of Products Subjected to Additional Manipulations—In repackaging, diluting, or mixing a product with another product, the pharmacist may become responsible for its stability.

REPACKAGING—In general, repackaging is inadvisable. However, if repackaging is necessary, the manufacturer should be consulted concerning potential problems. In the filling of prescriptions, it is essential that suitable containers be used. Appropriate storage conditions and, where appropriate, an expiration date, should be indicated on the label of the prescription container. Single-unit packaging calls for care and judgment, and for strict observance of the following guidelines: (1) use appropriate packaging materials; (2) where stability data on the new package are not available, repackage at any one time only sufficient stock for a limited time; (3) include on the unit-dose label a lot number and an appropriate expiration date; (4) where a sterile product is repackaged from a multiple-dose vial into unit-dose (disposable) syringes, discard the latter if not used within 24 hours, unless data are available to support longer storage; (5) where quantities are repackaged in advance of immediate needs, maintain suitable repackaging records showing name of manufacturer, lot number, date, and designation of persons responsible for repackaging and for checking; (6) where safety closures are required, use container closure systems that ensure compliance with compendial and regulatory standards for storage.

DILUTION OR MIXING—Where a product is diluted, or where two products are mixed, the pharmacist should observe good professional and scientific procedures to guard against incompatibility and instability. For example, tinctures such as those of belladonna and digitalis contain high concentrations of alcohol to dissolve the active ingredient(s), and they may develop a precipitate if they are diluted or mixed with aqueous systems. Pertinent technical literature and labeling should be consulted routinely; it should be current literature, because at times formulas are changed by the manufacturer. If a particular combination is commonly used, consultation with the manufacturer(s) is advisable. Since the chemical stability of extemporaneously prepared mixtures is unknown, the use of such combinations should be discouraged; if such a mixture involved an incompatibility